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(54) Title: TRIACETIN AS A TRANSDERMAL PENETRATION ENHANCER (57) Abstract <p>A composition and method for enhancing transdermal penetration of a basic drug are described. The composition comprises a matrix patch comprising an effective amount of a basic drug, preferably having a pK_a of about 8.0 or greater, an effective amount of a penetration enhancer consisting essentially of triacetin, and a polymer layer preferably comprising a pressure-sensitive adhesive. A preferred basic drug is oxybutynin and acid addition salts thereof. The method for enhancing transdermal penetration comprises applying the matrix patch to a selected area of skin.</p>		

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5 "TRIACETIN AS A TRANSDERMAL PENETRATION ENHANCER"

Field of the Invention

10 The present invention relates generally to a composition and method for enhancing the delivery of bioactive agents across biological membranes including skin or mucosa. More particularly, the invention relates to the use of triacetin (glyceryl triacetate) to enhance the transdermal or transmucosal delivery of
15 a basic drug having a pK_a of about 8.0 or greater, such as oxybutynin.

Background of the Invention

20 The oral administration of drugs as currently employed is unsatisfactory for a number of reasons. First, drugs with short half lives require frequent dosing (2 to 4 times daily), which can lead to inadequate compliance by the patient. Second, the short plasma half life of the drug and frequent dosing
25 regimen result in "peaks" and "valleys" in the plasma concentration profile, which increases the likelihood of adverse side effects associated with the peak concentration as well as lapse of therapeutic effectiveness toward the end of the dosing interval. Third, the potential effect of hepatic first pass
30 metabolism associated with oral administration could lead to poor bioavailability of the drug. Thus, an effective and consistent drug delivery system that overcomes these disadvantages would be far superior to the current oral regimen.
35

Transdermal delivery of drugs provides many advantages over conventional oral administration. Advantages of transdermal systems include convenience, uninterrupted therapy, improved patient compliance,
40 reversibility of treatment (by removal of the system from the skin), elimination of "hepatic first pass" effect, a high degree of control over blood concentration of the drug, and improved overall therapy.

5 Although transdermal systems have many
advantages, most drugs are not amenable to this mode
of administration due to the well known barrier
properties of the skin. Molecules moving from the
environment into and through intact skin must first
10 penetrate the stratum corneum, the outer horny layer
of the skin, and any material on its surface. The
molecule must then penetrate the viable epidermis and
the papillary dermis before passing through the
capillary walls and into systemic circulation. Along
15 the way, each of the above-mentioned tissues will
exhibit a different resistance to penetration by the
same molecule. However, it is the stratum corneum, a
complex structure of compact keratinized cell remnants
separated by extracellular lipid domains, that
20 presents the greatest barrier to absorption of topical
compositions or transdermally administered drugs.
Compared to the oral or gastric mucosa, the stratum
corneum is much less permeable to outside molecules.

 The flux of a drug across the skin can be
25 increased by changing either (a) the resistance (the
diffusion coefficient), or (b) the driving force (the
solubility of the drug in the stratum corneum and
consequently the gradient for diffusion). Many
enhancer compositions have been developed to change
30 one or both of these factors. U.S. Patent Numbers
4,006,218; 3,551,154; and 3,472,931, for example,
respectively describe the use of dimethylsulfoxide
(DMSO), dimethyl formamide (DMF), and N,N-
dimethylacetamide (DMA) for enhancing the absorption
35 of topically applied drugs through the stratum
corneum. Combinations of enhancers consisting of
diethylene glycol monoethyl or monomethyl ether with
propylene glycol monolaurate and methyl laurate are
disclosed in U.S. Patent No. 4,973,468 as enhancing
40 the transdermal delivery of steroids such as
progestogens and estrogens. A dual enhancer

5 consisting of glycerol monolaurate and ethanol for the
transdermal delivery of drugs is shown in U.S. Patent
No. 4,820,720. U.S. Patent No. 5,006,342 lists
numerous enhancers for transdermal drug administration
10 consisting of fatty acid esters or fatty alcohol
ethers of C₂ to C₄ alkanediols, where each fatty
acid/alcohol portion of the ester/ether is of about 8
to 22 carbon atoms. U.S. Patent No. 4,863,970 shows
penetration-enhancing compositions for topical
15 application comprising an active permeant contained in
a penetration-enhancing vehicle containing specified
amounts of one or more cell-envelope disordering
compounds such as oleic acid, oleyl alcohol, and
glycerol esters of oleic acid; a C₂ or C₃ alkanol; and
an inert diluent such as water.

20 Triacetin is known to be a solvent for
solubilizing or diluting a drug and/or other
components of drug delivery systems. For example,
Mahjour et al., U.S. Patent No. 4,879,297, disclose
triacetin as a solvent in an enhancer system of
25 propylene glycol and linoleic acid. Increasing
amounts of triacetin and corresponding decreasing
amounts of linoleic acid in the enhancer formulations
correlate with decreasing flux and increasing lag time
for permeation of the drug oxymorphone, suggesting
30 that triacetin is relatively unimportant in the
enhancer formulation. As another example, Ebert et
al., WO9325168-A1, disclose triacetin as a solvent, in
a list of many other solvents, to be used along with a
cell-envelope disordering compound for the delivery of
35 clonidine, progesterone, testosterone, and other
drugs. Other patent documents that describe triacetin
as a solvent include U.S. Patent No. 4,908,389; U.S.
Patent No. 5,019,395; U.S. Patent No. 4,666,926; U.S.
Patent No. 4,857,313; U.S. Patent No. 4,789,547; U.S.
40 Patent No. 4,814,173; U.S. Patent No. 4,783,450;

5 EP-387647-A; JP63255227-A; JP62240628-A; and
JP62215537-A.

Triacetin is also known as a plasticizer. For
example, Edgren et al., U.S. Patent No. 5,160,743,
teach the use of triacetin as a conventional
10 plasticizer to be used with an emulsifying agent in
tablets, capsules, powders, and the like for
gastrointestinal release of drugs. Other patent
documents and publications that disclose use of
triacetin as a plasticizer include Lin et al., 8
15 Pharm. Res. 1137 (1991); WO 9313753; EP 509335-A1; and
JP3083917-A.

Triacetin has also been described to function as
an antimicrobial agent. Allen, U.S. Patent No.
4,895,727, teaches that triacetin has activity as an
20 antifungal agent.

Triacetin has further been stated to contain
activity as an absorption accelerator. Ikeda et al.,
WO9309783-A1, disclose a piroxicam-containing plaster
for achieving an anti-inflammatory and analgesic
25 effect due to absorption of piroxicam through the skin
and state that triacetin enhances percutaneous
absorption of piroxicam. The plaster is composed of a
water-soluble polymeric adhesive; a glycol compound
such as glycerin or propylene glycol; a cross-linking
30 agent; water; an inorganic powder; and a surfactant,
such as polyoxyethylene sorbitol monooleate,
polyoxyethylene monooleate, sorbitol monooleate, or
polyoxyethylene castor oil. It is further stated
that, if necessary, penetration enhancers,
35 preservatives, antioxidants, flavoring agents, and
colorants can also be added to the formulation. The
glycols and surfactants are classic solvents and cell-
envelope disordering compounds known in the art of
penetration enhancement, e.g. U.S. Patent No.
40 4,855,294, thus the observed effects appear to result

5 from the combination of glycol, surfactant, and triacetin.

Japanese patent document JP05148141-A describes a two-layer percutaneous absorption preparation containing an adhesive, isosorbide dinitrate, and an
10 absorption accelerator. The absorption accelerators are stated to be glyceryl triesters wherein the fatty acid esters have chain lengths of 1 to 4 carbon atoms, triacetin being preferred. It should be recognized that isosorbide dinitrate has solubilizing properties
15 of its own, i.e. it is a neutral, "solvent-acting drug," Sablotsky et al., U.S. Patent No. 5,186,938. Other vasodilators, such as nitrate esters ($-C-O-NO_2$) characterized by a sequence of carbon-oxygen-nitrogen and nitrite esters characterized by a ($-C-O-NO$)
20 sequence, are among these solvent-acting drugs, including glyceryl trinitrate (erroneously called nitroglycerin according to its widespread and official designation), mannitol hexanitrate, erythritol tetranitrate, and pentaerythritol tetranitrate. Thus,
25 the penetration enhancing effect of triacetin reported by JP05148141-A is shown only in conjunction with a neutral, solvent-acting drug.

What has not been previously shown is that triacetin is by itself an effective penetration
30 enhancer for promoting the transdermal delivery of non-solvent-acting drugs, particularly of basic drugs having a pK_a of about 8.0 or greater and their acid addition salts. In view of the foregoing, it will be appreciated that compositions and methods for
35 enhancing penetration of such basic drug and their acid addition salts would be a significant advancement in the art.

Objects and Summary of the Invention

40 It is an object of the present invention to provide a composition and a method for enhancing

5 percutaneous delivery of a basic drug through the skin or mucosa.

It is also an object of the invention to provide a composition and method for enhancing transdermal delivery of the basic drug oxybutynin or an acid
10 addition salt thereof through the skin or mucosa.

It is another object of the invention to provide a composition and method for enhancing transdermal delivery of a basic drug having a pK_a of 8.0 or greater, such as oxybutynin or an acid addition salt
15 thereof, using triacetin as a penetration enhancer for permeating the skin or mucosa with the drug.

These and other objects are accomplished by providing a matrix patch for enhancing the rate of transdermal penetration of a basic drug having a pK_a of about 8.0 or greater comprising
20

- (a) a biocompatible polymer layer;
- (b) an effective amount of a percutaneously absorbable basic drug having a pK_a of about 8.0 or greater; and
- 25 (c) an effective amount of a permeation enhancer consisting essentially of triacetin.

Preferred basic drugs having a pK_a of 8.0 or greater include oxybutynin, scopolamine, fluoxetine, epinephrine, morphine, hydromorphone, atropine,
30 cocaine, buprenorphine, chlorpromazine, imipramine, desipramine, methylphenidate, methamphetamine, lidocaine, procaine, pindolol, nadolol, carisoprodol, and acid addition salts thereof. Oxybutynin and acid addition salts thereof are particularly preferred.

Preferably, the matrix patch comprises about 0.1% to about 50% by weight triacetin, more preferably about 1% to about 40% by weight triacetin, and most preferably about 2% to about 20% by weight triacetin. The polymer layer is preferably an adhesive, but can
40 also be laminated to an adhesive layer or used with an overlay adhesive. Suitable polymers include acrylics,

5 vinyl acetates, natural and synthetic rubbers, ethylenevinylacetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized weight polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof.

10 Acrylic copolymer adhesives are preferred. The matrix patch can also contain diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof provided that such additives do not alter the basic and novel

15 characteristics of the matrix patch.

The method of enhancing transdermal penetration of a basic drug comprises applying the matrix patch described above to a selected application situs.

20 Detailed Description of the Invention

Before the present composition and method for enhancing transdermal delivery of a basic drug, such as oxybutynin, and acid addition salts thereof are disclosed and described, it is to be understood that

25 this invention is not limited to the particular process steps and materials disclosed herein as such process steps and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing

30 particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this

35 specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a drug delivery device containing "a drug" includes a mixture of two or more

40 drugs, reference to "an adhesive" includes reference to one or more of such adhesives, and reference to "an

5 excipient" includes reference to a mixture of two or more of such excipients.

 In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

10 As used herein, the terms "enhancement", "penetration enhancement" or "permeation enhancement" mean an increase in the permeability of a biological membrane (*i.e.* skin or mucosa) to a drug, so as to increase the rate at which the drug permeates through the membrane. "Permeation enhancer," "enhancer,"
15 "penetration enhancer," or similar term means a material that achieves such permeation enhancement, and an "effective amount" of an enhancer means an amount effective to enhance penetration through the skin or mucosa of a selected agent to a selected
20 degree. The enhanced permeation as effected through the use of such enhancers can be observed, for example, by measuring the rate of diffusion of the drug through animal or human skin using a diffusion
25 cell apparatus. Such a diffusion cell is described by Merritt et al., Diffusion Apparatus for Skin Penetration, 1 J. of Controlled Release 61 (1984), incorporated herein by reference.

 As used herein, "transdermal" or "percutaneous"
30 delivery means delivery of a drug by passage into and through the skin or mucosal tissue. Hence the terms "transdermal" and "transmucosal" are used interchangeably unless specifically stated otherwise. Likewise the terms "skin," "derma," "epidermis,"
35 "mucosa," and the like shall also be used interchangeably unless specifically stated otherwise.

 By the term "permeant" or "drug" is meant any chemical material or compound suitable for transdermal or transmucosal administration which exists in the
40 appropriate free base or acid addition salt form and induces a desired biological or pharmacological effect

5 by transdermal delivery. Such substances include the
broad classes of compounds normally delivered through
body surfaces such as the skin. In general, this
includes therapeutic agents in all of the major
therapeutic areas including, but not limited to, anti-
10 infectives such as antibiotics and antiviral agents,
analgesics and analgesic combinations, anorexics,
antidiarrheals, antihistamines, anti-inflammatory
agents, antimigraine preparations, antimotion sickness
agents, antinauseants, antineoplastics,
15 antiparkinsonism drugs, antipruritics, antipsychotics,
antipyretics, antispasmodics including
gastrointestinal and urinary, anticholinergics,
sympathomimetics, xanthine derivatives, cardiovascular
preparations including calcium channel blockers, beta-
20 blockers, antiarrhythmics, antihypertensives,
diuretics, vasodilators including general coronary,
peripheral and cerebral, central nervous system
stimulants including cough and cold preparations,
decongestants, diagnostics, hormones,
25 immunosuppressives, muscle relaxants,
parasympatholytics, parasympathomimetics,
psychostimulants, sedatives and tranquilizers. The
term "permeant" or "drug" is also meant to include
mixtures. By mixtures is meant combinations of
30 permeants from different categories, mixtures of
permeants from the same category, and mixtures of free
base and salt forms of the same or different permeants
from the same or different categories.

By "basic drug" is meant a drug or permeant that
35 is a free base or an acid addition salt thereof.
Preferred basic drugs contain an amino group that
provides the drug with a basic character. More
preferred are strongly basic drugs with a pK_a of about
8.0 or greater. Preferred examples of basic drugs
40 that can be delivered by the penetration enhancing
system of the present invention include oxybutynin,

5 scopolamine, fluoxetine, epinephrine, morphine,
hydromorphone, atropine, cocaine, buprenorphine,
chlorpromazine, imipramine, desipramine,
methylphenidate, methamphetamine, lidocaine, procaine,
10 pindolol, nadolol, carisoprodol, and acid addition
salts thereof. Oxybutynin and acid addition salts
thereof are more preferred.

By "effective amount" of a drug or permeant is
meant a nontoxic but sufficient amount of a compound
to provide the desired local or systemic effect. An
15 "effective amount" of permeation enhancer as used
herein means an amount selected so as to provide the
desired increase in membrane permeability and,
correspondingly, the desired depth of penetration,
rate of administration, and amount of drug.

20 By "drug delivery system," "drug/enhancer
composition," or any similar terminology is meant a
formulated composition containing the drug to be
transdermally delivered in combination with a
penetration enhancer. Other pharmaceutically
25 acceptable materials or additives can also be
contained in the drug/enhancer composition, such as a
diluent, skin-irritation reducing agent, carrier or
vehicle, excipient, plasticizer, emollient, or other
additive and mixtures thereof provided that such
30 additives do not materially affect the basic and novel
characteristics of the matrix patch.

By the term "matrix," "matrix system," or "matrix
patch" is meant an active permeant or drug dissolved
or suspended in a biocompatible polymeric phase,
35 preferably a pressure sensitive adhesive, that can
also contain other ingredients or in which the
enhancer is also dissolved or suspended. This
definition is meant to include embodiments wherein
such polymeric phase is laminated to a pressure
40 sensitive adhesive or used with an overlay adhesive.
A matrix system usually and preferably comprises an

5 adhesive layer having an impermeable film backing
laminated onto the distal surface thereof and, before
transdermal application, a release liner on the
proximal surface of the adhesive. The film backing
protects the polymeric phase of the matrix patch and
10 prevents release of the drug and/or enhancer to the
environment. The release liner functions similarly to
the impermeable backing, but is removed from the
matrix patch prior to application of the patch to an
application situs. Matrix patches are known in the
15 art of transdermal drug delivery to routinely contain
such backing and release liner components, and matrix
patches according to the present invention should be
considered to comprise such backing and release liner
or their functional equivalents. U.S. Patent No.
20 5,122,383 describes such backing and release liner and
is hereby incorporated by reference. A matrix system
therefore is a unit dosage form of a drug composition
in a polymeric carrier, also containing the enhancer
and other components which are formulated for
25 maintaining the drug composition in the polymeric
layer in a drug transferring relationship with the
derma, i.e. the skin or mucosa. A matrix patch is
distinguished from a "liquid reservoir patch," wherein
an active permeant or drug is dissolved in a gelled
30 liquid contained in an occlusive device having an
impermeable back surface and an opposite surface
configured appropriately with a permeable membrane and
adhesive for transdermal application. E.g., U.S.
Patent No. 4,983,395.

35 As used herein, "application situs" means a site
suitable for topical application with or without the
means of a mechanical sustained release device, patch,
or dressing, e.g. behind the ear, on the arm, back,
chest, abdomen, leg, top of foot, etc.

40 As described above, the present invention
comprises a matrix patch for enhancing transdermal

5 delivery of a basic drug having a pK_a of about 8.0 or greater comprising

- (a) an biocompatible polymeric layer;
- (b) an effective amount of a percutaneously absorbable basic drug having a pK_a of about 8.0 or greater; and
- 10 (c) an effective amount of a permeation enhancer consisting essentially of triacetin.

It is surprising and unexpected that triacetin is effective in enhancing transdermal penetration of basic drugs, particularly those having a pK_a of about 8.0 or above, but not of neutral or acidic drugs. Of these basic drugs for which permeation is enhanced by triacetin, oxybutynin free base and acid addition salts thereof are preferred. It is further surprising that, although triacetin is effective as a penetration enhancer for basic drugs, such as oxybutynin free base, in matrix patch formulations, no penetration enhancement of basic drugs (including oxybutynin) or other drugs has been observed with liquid reservoir patches containing gelled drug formulations.

Suitable polymers that can be used in the biocompatible polymeric layer of the matrix patch include pressure-sensitive adhesives suitable for long-term contact with the skin. Such adhesives must be physically and chemically compatible with the drug and enhancer, and with any carriers and/or vehicles or other additives incorporated into the drug/enhancer composition. Suitable adhesives for use in the matrix patch include acrylic adhesives including cross-linked and uncross-linked acrylic copolymers; vinyl acetate adhesives; natural and synthetic rubbers including polyisobutylenes, neoprenes, polybutadienes, and polyisoprenes; ethylenevinylacetate copolymers; polysiloxanes; polyacrylates; polyurethanes; plasticized weight polyether block amide copolymers, and plasticized styrene-rubber block copolymers.

5 Preferred contact adhesives for use in the matrix patch herein are acrylic adhesives, such as TSR (Sekisui Chemical Co., Osaka, Japan) and DuroTak® adhesives (National Starch & Chemical Co., Bridgewater, N.J.), and polyisobutylene adhesives such
10 as ARcare™ MA-24 (Adhesives Research, Glen Rock, Pennsylvania).

In use, the matrix patch contains a distal backing laminated on the polymer layer. The distal backing defines the side of the matrix patch that
15 faces the environment, i.e., distal to the skin or mucosa. The backing layer functions to protect the matrix polymer layer and drug/enhancer composition and to provide an impenetrable layer that prevents loss of drug to the environment. Thus, the material chosen
20 for the backing should be compatible with the polymer layer, drug, and enhancer, and should be minimally permeable to any components of the matrix patch. Advantageously, the backing can be opaque to protect components of the matrix patch from degradation from
25 exposure to ultraviolet light. Further, the backing should be capable of binding to and supporting the polymer layer, yet should be pliable to accommodate the movements of a person using the matrix patch. Suitable materials for the backing include metal
30 foils, metalized polyfoils, composite foils or films containing polyester such as polyester terephthalate, polyester or aluminized polyester, polytetrafluoroethylene, polyether block amide copolymers, polyethylene methyl methacrylate block
35 copolymers, polyurethanes, polyvinylidene chloride, nylon, silicone elastomers, rubber-based polyisobutylene, styrene, styrene-butadiene and styrene-isoprene copolymers, polyethylene, and polypropylene. A thickness of about 0.0005 to 0.01
40 inch is preferred. The release liner can be made of

5 the same materials as the backing, or other suitable films coated with an appropriate release surface.

The matrix patch can further comprise various additives in addition to the polymer layer, basic drug, and triacetin-containing penetration enhancer
10 that are the fundamental components of the transdermal drug delivery system. These additives are generally those pharmaceutically acceptable ingredients that are known in the art of drug delivery and, more particularly, in the art of transdermal drug delivery
15 provided that such additive ingredients do not materially alter the basic and novel characteristics of the matrix patch. For example, suitable diluents can include mineral oil, low molecular weight polymers, plasticizers, and the like. Many
20 transdermal drug delivery formulations have a tendency to cause skin irritation after prolonged exposure to the skin, thus addition of a skin irritation reducing agent aids in achieving a composition that is better tolerated by the skin. A preferred skin irritation
25 reducing agent is glycerin, U.S. Patent No. 4,855,294. It is however notable that other so-called acceleration promoters or permeation enhancer components such as solvents and cell-envelope disordering compounds are not necessary, or even
30 desired, in the present invention.

For delivery of the basic drug according to the present invention, the matrix patch device containing a polymer layer, basic drug such as oxybutynin, and triacetin-containing penetration enhancer is brought
35 in contact with the skin or mucosa at a selected application situs and is held in place by a suitable pressure-sensitive adhesive. Preferably, the polymer layer of the matrix patch is an adhesive, but the polymer layer can also be laminated to an adhesive
40 layer or used with an overlay adhesive.

5 It is to be understood that while the invention
has been described in conjunction with the preferred
specific embodiments thereof, that which follows is
intended to illustrate and not limit the scope of the
invention. Other aspects of the invention will be
10 apparent to those skilled in the art to which the
invention pertains.

Experimental

Skin Flux Studies

15 In vitro human cadaver skin flux studies were
conducted using modified Franz non-jacketed permeation
cells. The temperature of the cells was maintained at
32°C by placing the cells in a circulating water bath
positioned over a stirring module. The epidermal
membrane was separated from the human cadaver whole
20 skin by the heat-separation method of Kligman &
Christopher, 88 Arch. Dermatol. 702 (1963), hereby
incorporated by reference, involving treating the full
thickness skin at 60°C for 60 seconds, after which
time the stratum corneum and the epidermis (epidermal
25 membrane) were gently peeled from the dermis.

For skin flux studies of matrix devices, the
epidermal membrane was cut into rectangular strips,
and the matrix device was cut into 0.96 cm² circular
discs. The release liner was peeled from the disc,
30 and the disc was laminated onto the stratum corneum
surface of the epidermal membrane to form a skin-
matrix laminate. The skin-matrix laminate was then
loaded between the donor and receiver compartments of
a diffusion cell with the epidermal side facing the
35 receiver compartment. The laminate was clamped in
place, and the receiver compartment was then filled
with an appropriate receiving solution for a selected
drug. The receiving solution was selected such that
40 the drug was stable in the solution, the subsequent
assay of the drug was not interfered with, and
solubility of the drug was adequate to ensure sink

5 conditions throughout the experiment. The diffusion
cell was then placed in a circulating water bath
calibrated to maintain the skin surface temperature at
32 \pm 1°C. At predetermined sampling intervals, the
entire contents of the receiver compartment were
10 collected for drug quantitation, and the receiver
compartment was filled with fresh receiving solution,
taking care to eliminate any air bubbles at the
skin/solution interface.

For skin flux studies of gel formulations (*i.e.*,
15 for liquid reservoir patch designs), the epidermal
membrane was cut and placed between two halves of the
permeation cell with the stratum corneum facing the
donor compartment. The skin was allowed to hydrate at
32°C overnight with 0.02% (w/v) sodium azide solution
20 in the receiver compartment. The following morning,
75 μ l of a gelled formulation was placed into a cavity
created by placing a polytetrafluoroethylene washer
over the stratum corneum surface. The cavity was then
occluded by clamping an occlusive backing over the
25 washer and gel. An appropriate receiving solution for
a selected drug was placed in the receiver compartment
in contact with the dermal side of the epidermis. The
solution in the receiver compartment was selected such
that the drug was stable in the solution, the
30 subsequent assay of the drug was not interfered with,
and solubility of the drug was adequate to ensure sink
conditions throughout the experiment. At
predetermined sampling intervals, the entire contents
of the receiver compartment were collected for drug
35 quantitation and the receiver compartment was filled
with fresh receiving solution, taking care to
eliminate any air bubbles at the skin/solution
interface.

The cumulative amount of drug permeating through
40 the epidermal membrane, Q_t (μ g/cm²), at any time t was

5 determined from the following formula:

$$Q_t = \sum_{n=0}^t (C_n * V) / A$$

where C_n is the concentration ($\mu\text{g/ml}$) of the drug in the receiver sample for the corresponding sample time, V is the volume of fluid in the receiver chamber (~ 6.3 10 cm^3), and A is the diffusional area of the cell (0.64 cm^2). The slope of the best fit line to the plot of Q_t vs. t gives the steady state flux (J_{ss} , $\mu\text{g/cm}^2/\text{hr}$); the intercept of this line on the time axis give the lag time (t_L, h).

15

Example 1

Oxybutynin free base, $\text{pKa} = 10.3$, is a strongly basic drug administered transdermally for antispasmodic and anticholinergic therapy. Matrix 20 patches containing varying amounts of oxybutynin free base and penetration enhancers were prepared and tested as described above. The matrix systems consisted of 5 to 20% by weight of oxybutynin free base and 0 to 20% by weight of the enhancer contained 25 in a medical grade acrylic copolymer adhesive.

The matrix formulations were prepared as follows. First, the solids content of the adhesive was determined by weighing a small amount of the adhesive solution in a preweighed aluminum dish. The solvent 30 was evaporated by overnight drying in a convection oven maintained at 80°C and the weight of the residue (dry adhesive) and percent solid adhesive content of the solution were determined. Once the solids content was determined, a known weight of the acrylic 35 copolymer adhesive solution was weighed into a glass bottle. From the weight of the adhesive solution and the percent solid adhesive content, the amount of adhesive in the solution was calculated. Oxybutynin free base and enhancer were added to the bottle in

5 proportions to yield the selected final composition.
The bottle was then tightly capped, sealed with
laboratory film, and rotated overnight until all
ingredients had completely dissolved and the resultant
solution was visually clear.

10 Approximately 8 ml of the solution was then
dispensed on a silanized polyester release liner and
cast with a 10 mil gap casting knife. The casting was
then dried in a convection oven at 70°C for 15 minutes
to evaporate the solvent and to yield a dried film
15 approximately 0.002 inch thick. A 0.003 inch thick
polyethylene backing film was laminated onto the dried
adhesive film with a rubber roller. These matrix
laminates were then used to conduct *in vitro* skin flux
studies as described above. The results of the skin
20 flux experiments are presented in Table 1-3.

Table 1		
Formulation ^a A/D/E (%w/w)	Q_t (t=24 hours) ($\mu\text{g}/\text{cm}^2/\text{t}$) ^b	J_{ss} ($\mu\text{g}/\text{cm}^2/\text{hr}$) ^b
80/20/0	47.05 \pm 21.01	2.03 \pm 0.95
75/20/5	63.90 \pm 23.45	3.07 \pm 1.06
70/20/10	125.75 \pm 56.00	6.08 \pm 2.62
60/20/20	155.08 \pm 74.55	7.46 \pm 3.44

a A = adhesive = TSR; D = drug = oxybutynin; E
= enhancer = triacetin

b Mean \pm SD

Table 2		
Formulation ^a A/D/E (%w/w)	Q _t (t=24 hours) (μg/cm ² /t) ^b	J _{ss} (μg/cm ² /hr) ^b
80/20/0	28.12 ± 13.74	1.13 ± 0.52
70/20/10	84.41 ± 30.72	3.64 ± 1.23
60/20/20	132.31 ± 42.61	5.92 ± 1.85

a A = adhesive = DuroTak 87-2196; D = drug = oxybutynin free base; E = enhancer = triacetin

b Mean ± SD

Table 3		
Formulation ^a A/D/E (%w/w)	Q _t (t=24 hours) (μg/cm ² /t) ^b	J _{ss} (μg/cm ² /hr) ^b
85/15/0	61.57 ± 33.19	2.58 ± 1.39
75/15/10	135.36 ± 23.85	5.80 ± 0.90

a A = adhesive = ARcare MA-24; D = drug = oxybutynin free base; E = enhancer = triacetin

b Mean ± SD

These results show that triacetin significantly increases the skin flux of oxybutynin free base as compared to adhesive/oxybutynin free base controls that lack triacetin. These enhancement effects by triacetin were observed with all three adhesives tested in these matrix formulations. With TSR adhesive at 20% drug loading, the increase is approximately 50% with 5% (w/w) triacetin, 3-fold with 10% (w/w) triacetin, and almost 4-fold with 20% (w/w) triacetin, as compared to controls. With DuroTak® 87-2196 adhesive at 20% drug loading, the increase in skin flux is about 3-fold with 10% (w/w) triacetin and 5-fold with 20% (w/w) triacetin, as compared to controls. With ARcare® MA-24 adhesive at 15% drug

loading, a 2-fold increase in skin flux was observed with 10% (w/w) triacetin, as compared to controls.

Example 2

The activity of several well known enhancers for enhancing transdermal flux of oxybutynin free base was evaluated according to the procedure of Example 1, with the exception that these enhancers were substituted for triacetin. The results of *in vitro* skin flux tests are shown in Table 4.

Table 4			
Enhancer	Formulation ^a A/D/E (t/w/w)	Q, (t=24 hours) ($\mu\text{g}/\text{cm}^2/\text{t}$) ^b	J_{ss} ($\mu\text{g}/\text{cm}^2/\text{hr}$) ^b
None	80/20/0	47.05 \pm 21.01	2.03 \pm 0.95
Sorbitan Monooleate	70/20/10	42.47 \pm 21.63	1.92 \pm 0.98
N-methyl pyrrolidone	60/20/20	54.36 \pm 1.98	2.42 \pm 0.97
Lauryl alcohol	70/20/10	24.29 \pm 8.73	1.25 \pm 0.41
Isopropyl myristate	70/20/10	48.26 \pm 13.08	2.05 \pm 0.54
Glycerol monooleate	70/20/10	52.78 \pm 8.25	2.25 \pm 0.32

a A = adhesive = TSR; D = drug = oxybutynin free base;
E = enhancer

b Mean \pm SD

These results show that none of the well known penetration enhancers tested, sorbitan monooleate (ARLACEL 80, ICI Americas, Wilmington, Delaware), N-methyl pyrrolidone (Pharmasolve®, International Specialty Chemicals, Wayne, NJ), lauryl alcohol, isopropyl myristate, or glycerol monooleate, exhibited the ability to increase transdermal skin flux of the basic drug, oxybutynin free base, in a matrix system.

Example 3

Piroxicam is a weakly basic anti-inflammatory, analgesic, and antipyretic agent with a pKa of 6.3.

The activity of triacetin for enhancing transdermal flux of piroxicam was evaluated according to the procedure of Example 1, with the exception that piroxicam was substituted for oxybutynin. These results are shown in Table 5.

Table 5		
Expt. No.	Formulation ^a A/D/E (%w/w)	Q_t (t=24 hours) ($\mu\text{g}/\text{cm}^2/\text{t}$) ^b
1	99.75/0.25/0	0.56 \pm 0.30
	99.25/0.25/0.5	0.58 \pm 0.07
	97.75/0.25/2.0	0.32 \pm 0.08
	95.75/0.25/4.0	0.45 \pm 0.17
2	99.75/0.25/0	0.55 \pm 0.31
	99.25/0.25/0.5	0.27 \pm 0.15
	97.75/0.25/2.0	0.03 \pm 0.02
	95.75/0.25/4.0	0.18 \pm 0.04
3	99.75/0.25/0	0.60 \pm 0.20
	99.25/0.25/0.5	0.36 \pm 0.14
	97.75/0.25/2.0	0.42 \pm 0.09
	95.75/0.25/4.0	0.31 \pm 0.14

a A = adhesive = TSR; D = drug = piroxicam
free base; E = enhancer = triacetin

b Mean \pm SD

These results show that triacetin decreases the skin flux of piroxicam. These results strongly suggest that the flux enhancement of piroxicam in gels, cited in Ikeda et al., WO 9309783-A1, is not due to triacetin alone, but appear to be a result of the combination of glycol and surfactants.

5

Example 4

Liquid reservoir gel formulations containing oxybutynin free base and triacetin were tested as described above. Such liquid reservoir gel formulations were prepared in 10 ml quantities.

10

Ethanol, water, glycerin, and triacetin were mixed in selected proportions in a capped vial. Then, 400 mg of oxybutynin free base was added to the vial, and the vial was capped and ultrasonicated to completely dissolve the drug. Next, 0.3 g of modified

15

hydroxyethyl cellulose (NATROSOL PLUS 330CS, Aqualon, Wilmington, Delaware) as a gelling agent was added to the mixture and the contents were mixed thoroughly and gently rotated overnight to completely dissolve the gelling agent. The resulting gel was then used in the skin flux studies, the results of which are presented in Table 6.

20

Table 6			
Expt No.	Formulation Et/W/G/E (%w/w) ^a	Q_t (t=24 hr) ($\mu\text{g}/\text{cm}^2/\text{t}$) ^b	J_{ss} ($\mu\text{g}/\text{cm}^2/\text{hr}$) ^b
1	30/60/10/0	178.41 \pm 24.04	7.40 \pm 0.98
	30/58/10/2	191.54 \pm 35.48	7.91 \pm 1.48
	30/50/10/10	110.58 \pm 20.06	4.49 \pm 0.83
2	30/60/10/0	172.41 \pm 45.51	7.16 \pm 1.89
	30/58/10/2	144.05 \pm 40.63	5.94 \pm 1.68
	30/50/10/10	155.74 \pm 61.53	6.43 \pm 2.60
3	30/60/10/0	118.23 \pm 52.30	4.86 \pm 2.15
	30/58/10/2	65.27 \pm 10.81	2.65 \pm 0.44
	30/50/10/10	54.75 \pm 12.91	2.22 \pm 0.52

25

30

a Et = ethanol; W = water; G = glycerin; E = enhancer = triacetin

b Mean \pm SD

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These results show that triacetin does not enhance the flux of oxybutynin from a gel formulation such as could be used in a liquid reservoir device.

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5 The flux actually decreases with triacetin-containing systems, consistent with Mahjour et al., U.S. Patent No. 4,879,297. Thus, even though triacetin very effectively enhances penetration of oxybutynin from matrix formulations, triacetin fails to enhance
10 penetration of the same drug from reservoir formulations.

Example 5

The following formulations are exemplary of other
15 compositions within the scope of this invention with triacetin and other highly basic active permeants in matrix patches. Such matrix patches can be made according to the procedure of Example 1. Several different types of pressure sensitive, skin-
20 contacting, medical grade adhesives can be used, such as acrylic copolymer adhesives or "acrylic adhesive" (e.g., DuroTak 80-1196, National Starch; Gelva 737, Monsanto Co., St. Louis, Missouri), rubber based adhesives or "rubber adhesive" such as polyisobutylene
25 or "PIB adhesive" (e.g., Adhesive Research MA-24), and silicone based adhesives or "silicone adhesive" such as Dow Bio-PSA. All compositions are given in ranges expressed in in percent by weight.

Formulation 5-A

30	Morphine	0.1-2.5%
	Acrylic Adhesive	82.5-94.9%
	Triacetin	5.0-15.0%

Formulation 5-B

35	Hydromorphone	30.0-40.0%
	PIB Adhesive	55.0-68.0%
	Triacetin	2.0-20.0%

40

Formulation 5-C

	Scopolamine	2.0-10.0%
	PIB Adhesive	75.0-93.0%
45	Triacetin	5.0-15.0%

5	<u>Formulation 5-D</u>	
	Atropine	1.0-10.0%
	Silicone Adhesive	85.0-98.0%
	Triacetin	1.0-5.0%
10	<u>Formulation 5-E</u>	
	Cocaine	0.5-5.0%
	Acrylic Adhesive	80.0-94.5%
15	Triacetin	5.0-15.0%
	<u>Formulation 5-F</u>	
	Buprenorphine	0.5-5.0%
20	PIB Adhesive	85.0-97.0%
	Triacetin	2.5-10.0%
	<u>Formulation 5-G</u>	
25	Scopolamine	0.1-5.0%
	Acrylic Adhesive	90.0-96.4%
	Triacetin	1.0-5.0%
	<u>Formulation 5-H</u>	
30	Chlorpromazine	0.5-7.5%
	Acrylic Adhesive	78.5-94.5%
	Triacetin	1.0-20.0%
35	<u>Formulation 5-I</u>	
	Imipramine	0.5-5.0%
	Acrylic Adhesive	85.0-97.0%
	Triacetin	2.5-10.0%
40	<u>Formulation 5-J</u>	
	Desipramine	0.5-5.0%
	Acrylic Adhesive	87.5-94.0%
45	Triacetin	2.5-7.5%
	<u>Formulation 5-K</u>	
	Methylphenidate	0.1-1.0%
50	Silicone Adhesive	94.0-97.4%
	Triacetin	2.5-5.0%
	<u>Formulation 5-L</u>	
55	Methamphetamine	2.5-10.0%
	Acrylic Adhesive	82.5-95.0%
	Triacetin	2.5-7.5%

5	<u>Formulation 5-M</u>	
	Lidocaine	0.1-5.0%
	Acrylic Adhesive	90.0-98.9%
10	Triacetin	1.0-5.0%
	<u>Formulation 5-N</u>	
	Procaine	0.1-5.0%
15	PIB Adhesive	80.0-97.4%
	Triacetin	2.5-15.0%
	<u>Formulation 5-O</u>	
20	Pindolol	0.1-10.0%
	Acrylic Adhesive	65.0-94.9%
	Triacetin	5.0-25.0%
	<u>Formulation 5-P</u>	
25	Nadolol	0.1-10.5%
	Acrylic Adhesive	74.5-94.9%
	Triacetin	5.0-15.0%
	<u>Formulation 5-Q</u>	
30	Fluoxetine	5.0-40.0%
	Acrylic Adhesive	35.0-84.9%
	Triacetin	5.0-25.0%
35	<u>Formulation 5-R</u>	
	Fluoxetine	5.0-40.5%
	PIB Adhesive	55.5-90.0%
40	Triacetin	5.0-15.0%
	<u>Formulation 5-S</u>	
	Fluoxetine	5.0-40.5%
45	Silicone Adhesive	55.5-89.5%
	Triacetin	5.0-15.0%
	<u>Formulation 5-T</u>	
50	Fluoxetine	5.0-40.5%
	EVA copolymer	55.5-89.5%
	Triacetin	5.0-15.0%
	<u>Formulation 5-U</u>	
55	Fluoxetine	5.0-40.5%
	Styrene-Rubber Block Copolymer	55.5-89.5%
	Triacetin	5.0-15.0%

5 Formulation 5-V

	Carisoprodol	5.0-40.5%
	PIB Adhesive	55.5-89.5%
10	Triacetin	5.0-15.0%

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Claims

We claim:

1. A method of enhancing the rate of transdermal penetration of a basic drug having a pK_a of about 8.0 or greater comprising applying to a selected application situs a matrix patch comprising

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(a) a biocompatible polymer layer;

(b) an effective amount of a percutaneously absorbable basic drug having a pK_a of about 8.0 or greater; and

15

(c) an effective amount of a permeation enhancer consisting essentially of triacetin.

2. The method of claim 1 wherein said basic drug is a member selected from the group consisting of oxybutynin, scopolamine, fluoxetine, epinephrine, morphine, hydromorphone, atropine, cocaine, buprenorphine, chlorpromazine, imipramine, desipramine, methylphenidate, methamphetamine, lidocaine, procaine, pindolol, nadolol, carisoprodol, and acid addition salts thereof.

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3. The method of claim 2 wherein said effective amount of permeation enhancer comprises about 0.1% to about 50% by weight of triacetin.

25

4. The method of claim 3 wherein said polymer layer comprises an adhesive.

30

5. The method of claim 4 wherein said adhesive is a member selected from the group consisting of acrylics, vinyl acetates, natural and synthetic rubbers, ethylenevinylacetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized weight polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof.

35

6. The method of claim 5 wherein said basic drug is a member selected from the group consisting of oxybutynin and acid addition salts thereof.

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5 7. The method of claim 6 wherein said effective amount of permeation enhancer comprises about 1% to about 40% by weight of triacetin.

10 8. The method of claim 7 wherein matrix patch further comprises a member selected from the group consisting of diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof.

 9. The method of claim 8 wherein said basic drug is oxybutynin.

15 10. The method of claim 9 wherein said adhesive is an acrylic copolymer.

 11. The method of claim 10 wherein the permeation enhancer comprises about 2% to about 20% by weight of triacetin.

20 12. The method of claim 11 wherein said matrix patch comprises a skin irritation reducing agent, wherein said skin irritation reducing agent is glycerin.

25 13. The method of claim 3 wherein said polymer layer is laminated to an adhesive.

 14. The method of claim 3 wherein said polymer layer is overlaid with an adhesive.

30 15. A matrix patch for transdermal administration of a basic drug having a pK_a of about 8.0 or greater comprising

 (a) an biocompatible polymer layer;

 (b) an effective amount of a percutaneously absorbable basic drug having a pK_a of about 8.0 or greater; and

35 (c) an effective amount of a permeation enhancer consisting essentially of triacetin.

40 16. The matrix patch of claim 15 wherein said basic drug is a member selected from the group consisting of oxybutynin, scopolamine, fluoxetine, epinephrine, morphine, hydromorphone, atropine, cocaine, buprenorphine, chlorpromazine, imipramine,

5 desipramine, methylphenidate, methamphetamine,
lidocaine, procaine, pindolol, nadolol, carisoprodol,
and acid addition salts thereof.

10 17. The matrix patch of claim 16 wherein said
effective amount of permeation enhancer comprises
about 0.1% to about 50% by weight of triacetin.

18. The matrix patch of claim 17 wherein said
polymer layer comprises an adhesive.

15 19. The matrix patch of claim 18 wherein said
adhesive is a member selected from the group
consisting of acrylics, vinyl acetates, natural and
synthetic rubbers, ethylenevinylacetate copolymers,
polysiloxanes, polyacrylates, polyurethanes,
plasticized weight polyether block amide copolymers,
plasticized styrene-rubber block copolymers, and
20 mixtures thereof.

20. The matrix patch of claim 19 wherein said
basic drug is a member selected from the group
consisting of oxybutynin and acid addition salts
thereof.

25 21. The matrix patch of claim 20 wherein said
effective amount of permeation enhancer comprises
about 1% to about 40% by weight of triacetin.

30 22. The matrix patch of claim 21 wherein matrix
patch further comprises a member selected from the
group consisting of diluents, excipients, emollients,
plasticizers, skin irritation reducing agents,
carriers, and mixtures thereof.

23. The matrix patch of claim 22 wherein said
basic drug is oxybutynin.

35 24. The matrix patch of claim 23 wherein said
adhesive is an acrylic copolymer.

25. The matrix patch of claim 24 wherein the
permeation enhancer comprises about 2% to about 20% by
weight of triacetin.

40 26. The matrix patch of claim 25 wherein said
matrix patch comprises a skin irritation reducing

5 agent, wherein said skin irritation reducing agent is glycerin.

27. The matrix patch of claim 17 wherein said polymer layer is laminated to an adhesive.

10 28. The matrix patch of claim 17 wherein said polymer layer is overlaid with an adhesive.

AMENDED CLAIMS

5 [received by the International Bureau on 30 July 1996 (30.07.96):
original claims 1-28 replaced by amended claims 1-24 (3 pages)]

1. A method of enhancing the rate of transdermal
penetration of a basic drug having a pK_a of about 8.0 or
greater comprising applying to a selected application
10 situs a matrix patch comprising

(a) a biocompatible polymer layer, wherein said
biocompatible polymer is an adhesive selected from the
group consisting of acrylics, vinyl acetates, natural
and synthetic rubbers, ethylenevinylacetate copolymers,
15 polysiloxanes, polyacrylates, polyurethanes, plasticized
polyether block amide copolymers, plasticized styrene-
rubber block copolymers, and mixtures thereof;

(b) an effective amount of a percutaneously
absorbable basic drug having a pK_a of about 8.0 or
20 greater; and

(c) an effective amount of a permeation enhancer
consisting essentially of triacetin.

2. The method of claim 1 wherein said basic drug
is a member selected from the group consisting of
25 oxybutynin, scopolamine, fluoxetine, epinephrine,
morphine, hydromorphone, atropine, cocaine,
buprenorphine, chlorpromazine, imipramine, desipramine,
methylphenidate, methamphetamine, lidocaine, procaine,
pindolol, nadolol, carisoprodol, and acid addition salts
30 thereof.

3. The method of claim 2 wherein said effective
amount of permeation enhancer comprises about 0.1% to
about 50% by weight of triacetin.

4. The method of claim 3 wherein said basic drug
35 is a member selected from the group consisting of
oxybutynin and acid addition salts thereof.

5. The method of claim 4 wherein said effective
amount of permeation enhancer comprises about 1% to
about 40% by weight of triacetin.

40 6. The method of claim 5 wherein matrix patch
further comprises a member selected from the group

5 consisting of diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof.

7. The method of claim 6 wherein said basic drug is oxybutynin.

10 8. The method of claim 7 wherein said adhesive is an acrylic copolymer.

9. The method of claim 8 wherein the permeation enhancer comprises about 2% to about 20% by weight of triacetin.

15 10. The method of claim 9 wherein said matrix patch comprises a skin irritation reducing agent, wherein said skin irritation reducing agent is glycerin.

11. The method of claim 3 wherein said polymer layer is laminated to an adhesive.

20 12. The method of claim 3 wherein said polymer layer is overlaid with an adhesive.

13. A matrix patch for transdermal administration of a basic drug having a pK_a of about 8.0 or greater comprising

25 (a) an biocompatible polymer layer, wherein said biocompatible polymer is an adhesive selected from the group consisting of acrylics, vinyl acetates, natural and synthetic rubbers, ethylenevinylacetate copolymers, polysiloxanes, polyacrylates, polyurethanes, plasticized polyether block amide copolymers, plasticized styrene-rubber block copolymers, and mixtures thereof;

30 (b) an effective amount of a percutaneously absorbable basic drug having a pK_a of about 8.0 or greater; and

35 (c) an effective amount of a permeation enhancer consisting essentially of triacetin.

40 14. The matrix patch of claim 13 wherein said basic drug is a member selected from the group consisting of oxybutynin, scopolamine, fluoxetine, epinephrine, morphine, hydromorphone, atropine, cocaine, buprenorphine, chlorpromazine, imipramine, desipramine,

5 methylphenidate, methamphetamine, lidocaine, procaine, pindolol, nadolol, carisoprodol, and acid addition salts thereof.

15 15. The matrix patch of claim 14 wherein said effective amount of permeation enhancer comprises about 0.1% to about 50% by weight of triacetin.

16. The matrix patch of claim 15 wherein said basic drug is a member selected from the group consisting of oxybutynin and acid addition salts thereof.

15 17. The matrix patch of claim 16 wherein said effective amount of permeation enhancer comprises about 1% to about 40% by weight of triacetin.

20 18. The matrix patch of claim 17 wherein matrix patch further comprises a member selected from the group consisting of diluents, excipients, emollients, plasticizers, skin irritation reducing agents, carriers, and mixtures thereof.

19. The matrix patch of claim 18 wherein said basic drug is oxybutynin.

25 20. The matrix patch of claim 19 wherein said adhesive is an acrylic copolymer.

21. The matrix patch of claim 20 wherein the permeation enhancer comprises about 2% to about 20% by weight of triacetin.

30 22. The matrix patch of claim 21 wherein said matrix patch comprises a skin irritation reducing agent, wherein said skin irritation reducing agent is glycerin.

23. The matrix patch of claim 15 wherein said polymer layer is laminated to an adhesive.

35 24. The matrix patch of claim 15 wherein said polymer layer is overlaid with an adhesive.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 424/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,666,926 A (M. MAJHOUR ET AL.) 19 May 1987, column 1, line 45 through column 2, line 39 and column 4, lines 1-8.	1, 15
X	US 4,857,313 A (S. SONG) 15 August 1989, column 2, lines 54-65 and column 4, lines 13-38.	1, 15
X	WO 93/09783 A (S.S. PHARMACEUTICAL CO. LTD.) 27 May 1993, see entire document.	1, 15

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

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